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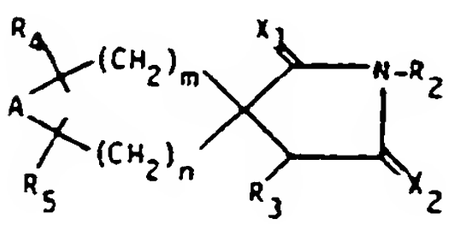
None

(58) Field of search
C2C

(54) Spirosuccinimide derivatives

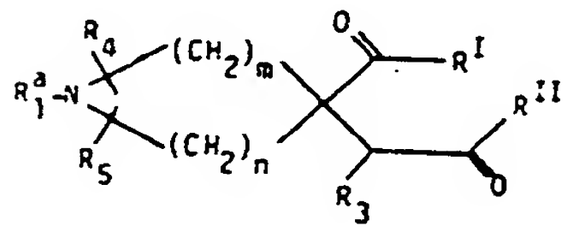
(57) Novel compounds of formula I



I

wherein A, R_2, R_5, X_1, X_2, m and n have various significances are useful in the treatment of senile dementia, Alzheimer's disease, Huntington's chorea, tardive diskinesia, hyperkinesia or mania.

Intermediates of the formula IV



are also claimed.

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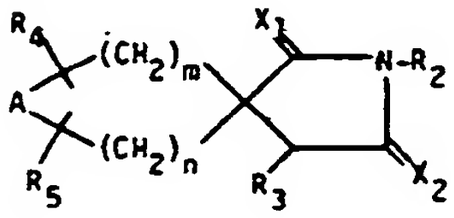
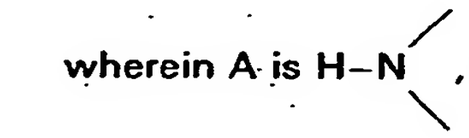
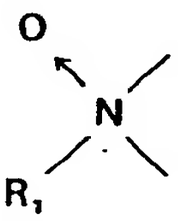
SPECIFICATION

Spirosuccinimide d rivatives

This invention relates to spirosuccinimides.

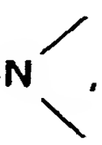
The present invention provides a compound of formula I



wherein A is  , or 

R_1 is (C_{1-6})alkyl, (C_{1-6})alkyl substituted by 1 to 6 halogens of atomic number from 9 to 35, (C_{3-6})alkenyl or-alkinyl, wherein the multiple bond is not adjacent to the nitrogen atom, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl(C_{1-2})alkyl, (C_{3-7})cycloalkyl(C_{1-2})alkyl substituted by hydroxy, (C_{1-4})alkoxy or (C_{2-5})alkanoyl, benzyl, tetrahydrobenzocycloheptenyl or a group of formula

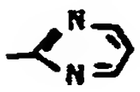
$-(CH_2)_r-X$

wherein r is 1, 2 or 3 or alternatively also O when A is  , and

X is hydroxy, mercapto, amino, (C_{1-4})alkoxy, phenoxy, benzoxy, (C_{1-4})alkylthio, phenylthio, benzylthio, (C_{1-4})alkylamino,phenylamino,benzylamino,cyano,formyl,carbamoyl,carbamoyl mono- or independently di-substituted by phenyl or (C_{1-4})alkyl,

 ,

sulfamoyl, sulfamoyl mono- or independently di-substituted by phenyl or (C_{1-4})alkyl, guanyl,



(C_{2-5})alkanoyl, (C_{2-5})alkanoyl independently substituted by 1 to 3 halogen atoms of atomic number from 9 to 35 or 2-oxo-pyrrolidinyl, benzoyl, cinnamoyl, nicotinoyl, dihydronicotinoyl, N–(C_{1-4})alkyl dihydronicotinoyl, alkoxycarbonyl with 2 to 5 carbon atoms, benzoxycarbonyl, (C_{1-4})alkoxyoxalyl, (C_{1-4})alkanoyloxy or benzoyloxy,

R_2 is hydrogen, (C_{1-6})alkyl, $(C_{1-6}$alkyl substituted by 1 to 6 halogen atoms of atomic number of 9 to 35, hydroxy(C_{1-4})alkyl, (C_{1-4})alkoxy(C_{1-4})alkyl, (C_{1-4})mercaptoalkyl, (C_{1-4})alkylthio(C_{1-4})alkyl, amino(C_{1-4})alkyl, mono- or independently di(C_{1-4})alkylamino(C_{1-4})alkyl, $(_{3-6})$alkenyl or alkinyl wherein the multiple bond is not adjacent to the nitrogen atom, (C_{3-7})cycloalkyl, $(C_{3-7}$cycloalkyl (C_{1-2})alkyl, phenyl or benzyl,

R_3 is hydrogen, (C_{1-4})alkyl, benzyl or benzyl substituted by halogen of atomic number of from 9 to 35 or methoxy,

R_4 and R_5 independently are hydrogen or (C_{1-4})alkyl,

X_1 and X_2 are independently oxygen or sulphur,

m and n indep ndently are 1,2, 3 or 4 with the proviso that m + n is not more than 6 with the proviso that X_1 and X_2 are not both oxygen when m and n are each 2,

A is $H-N\diagup\diagdown$ or $R_1-N\diagup\diagdown$ wherein R_1 is unsubstitut d (C_{1-6})alkyl, chloropropyl, hydroxypropyl, allyl,benzyl, ethoxycarbonyl, b nzoylalkyl and R_2 is hydrogen, unsubstitut d (C_{1-6})alkyl, allyl, phenyl or benzyl,

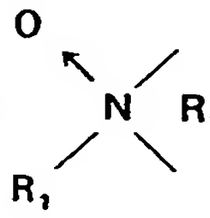
or an acid addition salt thereof.

As described hereinafter reference to a particular formula and definitions relating thereto implies reference also to any provisos in the definitions.

Any alkyl, alkoxy or alkylthio group preferably has 1 or 2 carbon atoms and especially 1 carbon atom. Halogen is preferably fluorine or chlorine. Where a group is substituted it may be poly substituted, preferably up to 3 substituents, unless stated otherwise.

R_1 is for example hydrogen, methyl, ethyl substituted by halogen, cyclopropylmethyl or cyano. R_2 is preferably ethyl m and n are preferably 2 and 2 respectively or 3 and 1 respectively.

Preferred compounds are compounds of formula I wherein A is as defined above and R_1 is (C_{1-4})alkyl, (C_{1-4})alkyl substituted by 1 to 6 halogen atoms of atomic number from 9 to 35, cyclopropylmethyl, (C_{3-7})cycloalkyl, cyano, cyanomethyl or formyl, R_2 is hydrogen, (C_{1-4})alkyl, (C_{1-4})alkyl substituted by 1 to 6 halogen atoms of atomic number from 9 to 35, or (C_{3-7})cycloalkyl, R_3, R_4 and R_5 are each hydrogen, X_1 and X_2 are independently oxygen or sulphur, m and n are each 2,with the provisos that

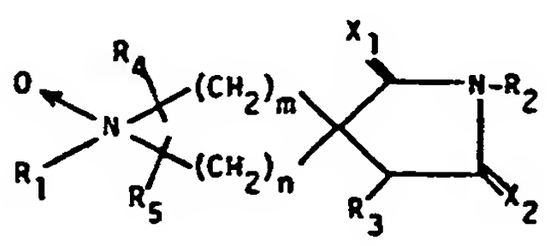
(i) when A is  R_1 is other than cyano or formyl, and

(ii) X_1 and X_2 are not both oxygen when A is $HN\diagup\diagdown$ or $R_1N\diagup\diagdown$

wherein R_1 is unsubstituted alkyl or chloropropyl and R_2 is hydrogen or unsubstituted alkyl, or an acid addition salt thereof.

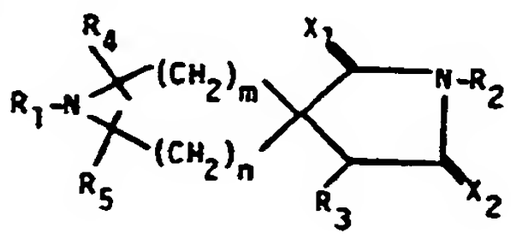
The present invention also provides a process for the production of a compound of formula I or an acid addition salt thereof,
which comprises

(a) for the production of a compound of formula Ia



Ia

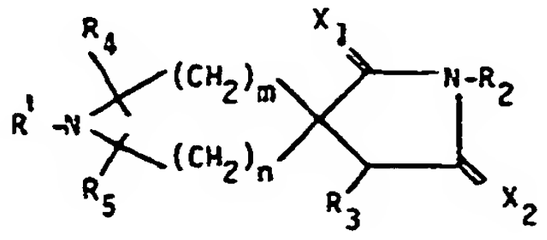
wherein R_{1-5}, X_1, X_2, m and n are as defined above, or an acid addition salt thereof, oxidizing an appropriate compound of of formula II



II

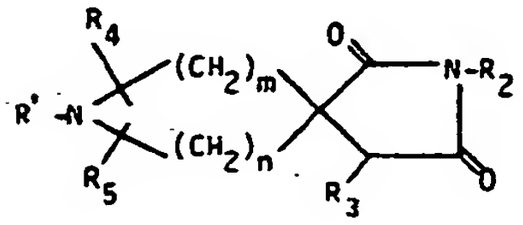
wherein R_{1-5}, X_1, X_2, m and n are as defined above, or an acid addition salt thereof,

(b) for the production of a compound of formula Ib



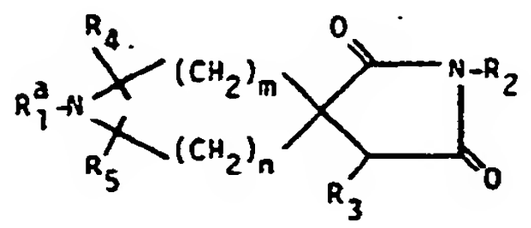
Ib

wherein R′ is hydrogen or R_1 as defined above, and R_{2-5}, X_1, X_2, m and n are as defined above with the provisos thereto and the further proviso that both X_1 and X_2 are not oxygen,
or an acid addition salt thereof,
replacing at least one oxo group by a thio group in an appropriate compound of formula III



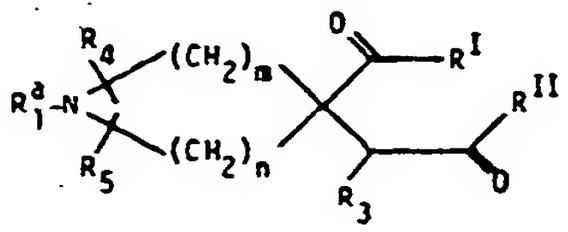
III

wherein R′, R_5, m and n are as defined above or an acid addition salt thereof,
(c) for the production of a compound of formula



Ic

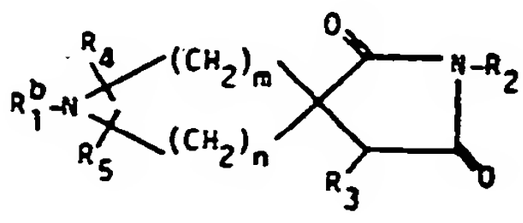
wherein R_{2-5}, m an n are as defined above, and R_1^a is hydrogen, (C_{1-6})alkyl,(C_{1-6})alkyl substituted by 1–6 halogens of atomic number of from 9 to 35, (C_{3-6})alkenyl or alkinyl, wherein the multiple bond is not adjacent to the nitrogen atom, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl(C_{1-2})alkyl, (C_{3-7})cycloalkyl(C_{1-2})alkyl substituted by hydroxy, (C_{1-4})alkoxy or (C_{2-5})alkanoyl, benzyl, tetrahydrobenzocycloheptenyl,
with the proviso that m and n are not both 2 when R_1^a is hydrogen, unsubstituted (C_{1-6})alkyl,hydroxypropyl,chloropropyl, allyl or benzyl and R_2 is hydrogen, (C_{1-6})alkyl, allyl, phenyl or benzyl,
or an acid addition salt thereof,
cyclising the product obtainable by condensing a compound of formula IV



wherein R_1^a, R_{3-5}, m and n are as defined above with respect to formula Ic, and R^I and R^{II} are independently leaving groups, with an appropriate compound of formula V

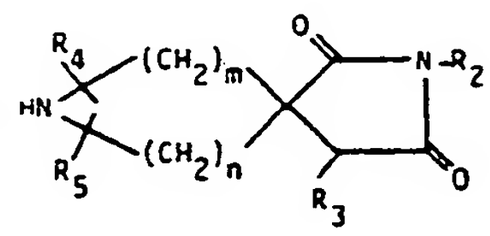
R_2-NH_2 V

wherein R_2 is as defined above with respect to formula Ic,
(d) for the production of a compound of formula Id



Id

wherein R_{2-5}, m and n are as defined above and
R_1^b is as defined above for R_1 with the proviso that m and n are not both 2 when R_1^b is unsubstituted (C_{1-6})alkyl, hydroxypropyl, chloropropyl, allyl, benzyl ethoxycarbonyl or benzoylalkyl and R_2 is hydrogen, unsubstituted(C_{1-6})alkyl, allyl, phenyl or benzyl,
or an acid addition salt thereof,
introducing a group of formula R_1^b into a compound of formula VI

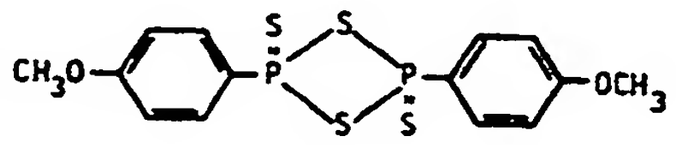


VI

wherein R_{2-5}, m and n are as defined above with respect to formula Id, and recovering the compound of formula I or an acid addition salt thereof.

Process (a) may be effected in conventional manner for the production of N-oxides using e.g. oxidising agents. Examples of oxidising agents include hydrogen peroxide or organic peracids such as chloroperbenzoic acid.

Process (b) is conveniently carried out using a conventional sulphur-containing agents used for analogous reactions, e.g. P_4S_{10} or a 2,4-dithiooxocyclo di-λ^5-phosphathiane e.g. the compound of formula



also called Lawesson Reagent.

The reaction may be effected in an inert solvent, e.g. at temperatures from about 50 and 150°C. Mixtures of compounds of formula Ib may be obtained e.g. compounds of formula Ib wherein
(i) X_1 and X_2 are both sulphur
(ii) X_1 is sulphur and X_2 is oxygen
(iii) X_1 is oxygen and X_1 is sulphur.
The compounds may be separated in conventional manner, e.g. by chromatography.

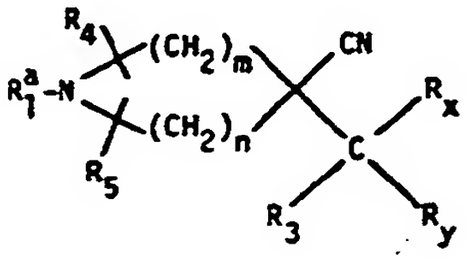
Process (c) may be effected in conventional manner for analogous cyclisations. The reaction is conveniently effected by warming to a high temperature, e.g. from about 150 to about 250°C, if desired in an inert solvent.

The reaction may be effected if desired in a closed vessel e.g. an autoclave. R^I and R^{II} may be for example hydroxy, (C_{1-4})alkoxy or amino.

Process (d) may be effected in conventional manner for the preparation of tertiary amines, e.g. by reaction with a compound of formula R_1^b–Y wherein Y is a leaving group, e.g. halogen or an organic sulphonic acid radical.

The compounds of formula I and their acid addition salts may be isolated and purified in conventional manner. The compounds of formula I may be converted into their acid addition salts in conventional manner and vice versa. Suitable acids for salt formation include hydrochloric acid, maleic acid and methane-sulphonic acid.

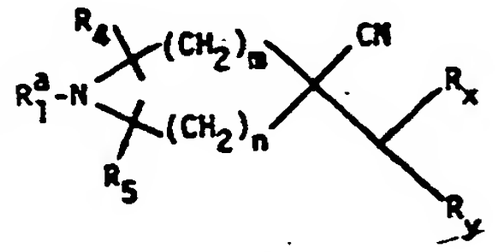
Starting materials of formula IV may for example be produced by reacting a compound of formula VII



VII

wherein R_1^a, R_3, R_4, R_5, m and n are as defined above with respect to formula IV, and R_x and R_y are independently cyano or lower alkoxycarbonyl, hydrolysed in acid conditions, decarboxylated and if desired treated with an alkanol, or amine or otherwise converted into another compound of formula IV.

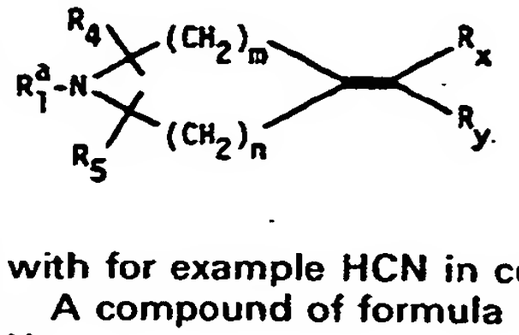
Compounds of formula VII wherein R_3 is other than hydrogen may be obtained by appropriately alkylating a compound of formula VIII



VIII

wherein R_1^a, R_4, R_5, R_x, R_y, m and n are as defined above, e.g. with an alkyl halide.

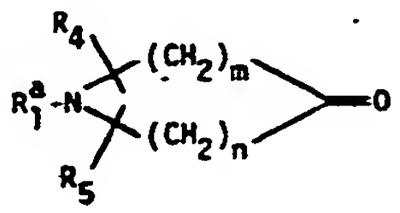
A compound of formula VIII may for example be produced by treating a compound of formula IX



IX

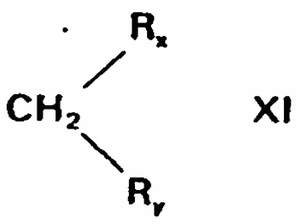
with for example HCN in conventional manner.

A compound of formula IX may for example be produced by reacting a compound of formula X



X

and an appropriate compound of formula XI



XI

in conventional manner.

The invention also provides groups of compounds comprising:

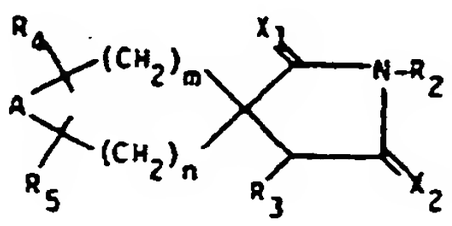
(a) compounds of formula III as defined above or an acid addition salt thereof

(b) compounds of formula Ib as defined above or an acid addition salt thereof

(c) compounds of formula Ia wherein R_1 is as defined above and when it contains the group X_1, this is hydroxy, alkoxy, phenoxy, formyl, optionally substituted alkanoyl, benzoyl, cinnamoyl, alkoxycarbonyl, benzoxycarbonyl, alkanoyloxy or benzoyloxy as defined above, and R_2 is hydrogen, alkyl, optionally substituted by halogen, alkoxyalkyl, hydroxyalkyl, alkenyl or alkinyl, cycloalkyl, cycloalkylalkyl, phenyl or benzyl as defined above, or an acid addition salt thereof.

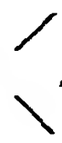
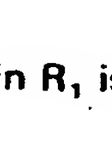
Insofar as the preparation of the starting materials is not particularly described these are known or may be prepared in conventional manner.

Furthermore we have found that the compounds of formula A



A

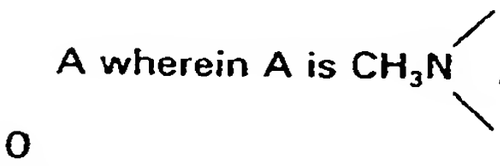
wherein X_1 and X_2 are each hydrogen, m and n are each 2,

A is  or  wherein R_1 is unsubstituted (C_{1-6})alkyl,

hydroxypropyl, chloropropyl, allyl, benyl, ethoxycarbonyl or benzoylalkyl, R_2 is hydrogen,

unsubstituted (C_{1-6}), alkyl, allyl, phenyl or benzyl and acid addition salt thereof are particularly indicated for use as pharmaceuticals. These compounds are in general known. Any compound which is not specifically known may b made in analogous manner to that described above.

Compounds of formula A wherein R_1 is hydroxypropyl, chloropropyl or ethoxycarbonyl have not been previously disclosed as having pharmacological activity. The compound of formula



A wherein A is CH_3N , R_2 is ethyl, R_2, R_3 and R_4 are each hydrogen,

X_1 and X_2 are each oxygen and m and n each 2 has been shown to be clinically useful as described in earlier filed copending patent applications. The remaining compounds have been in general disclosed as having pharmacological activity, e.g. cholinergic or analgesic activity, e.g. in German Patent 1,211,646 and E. Jucker et al, Arch. Pharm. (1961), *294*, 210–220, and Helv.Chem.Acta (1966), *49*, 1135–45.

We have now found that these compounds are useful for the treatment of senile dementia, Alzheimer's disease, Huntington's Chorea, tardive diskinsia, hyperkinesia and mania as indicated in activity in tests mentioned below.

The compounds of formula I and A and their acid addition salts, hereinafter referred to as compounds of the invention, exhibit pharmacologically activity and are therefore indicated for use as pharmaceuticals, e.g. for therapy.

In particular the compounds show activity in the following tests:–

(i) in the observation test in the mouse the compounds at doses from 1 to 300 mg/kg p.o. provoke a prolongation of the wake phase and an increased reactivity to external stimuli,

(ii) in the sleep/wake cycle test in chronically implanted rats the compounds at doses from about 1 to about 100 mg/kg p.o. increase the REM sleep phase, and

(iii) in the carbon-14 deoxyglucose rat test [according to the principles of L.Sokoloff, Journal of Cerebral Blood Flow and Metabolism 1981, *1*, 7–36, H.E. Savaki et al., Brain Research 1982, *233*, 347 and J.McCulloch et al.,Journal of Cerebral Blood Flow and Metabolism 1981, *1*, 133–136], the compounds at doses from about 1 to 300 mg/kg increase the carbon-14 deoxyglucose uptake in particular areas of the brain, particularly the limbic system.

The compounds of the invention are therefore indicated for use for the treatment of senile dementia, Alzheimer's disease, Huntington's chorea, tardive diskinesia, hyperkinesia, and mania.

An indicated total daily dosage is in the range from about 1 to about 100 mg of the compound, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing for example from about 0.2 to about 50 mg of the compound or in sustained release form.

The example 2 title compound is the preferred compound. The sensile dementia and Alzheimer's disease indications are the preferred indications.

Appropriate unit doses for oral administration contain for example about 0.5 to about 15 mg of the compounds, e.g. from 1 to 10 mg. Appropriate doses for parenteral administration contain for example about 0.2 to about 30 mg of the compounds, e.g. from 0.3 to 10 mg.

The compounds of the invention may be administered in free base form or as a pharmaceutically acceptable acid addition salt. Such salts may be prepared in conventional manner and exhibit the same order of activity as the free forms.

The present invention also provides a pharmaceutical composition comprising a composition of the invention in free base form or in pharmaceutically acceptable acid addition salt form in association with a pharmaceutical carrier or diluent.

The pharmaceutical compositions may be formulated in conventional manner and contain a compound of the invention alone or in admixture with a pharmaceutical carrier or diluent. Oral pharmaceutical compositions may be in the form of, for example, tablets, dispersible powders, granulates, capsules, sirups, suspensions, solutions or elixiers. Liquid forms may contain for example from about 0.1 to about 5 mg/ml, e.g. 0.5 to 2 mg/ml of a compound. Parenteral pharmaceutical forms may be for example solutions or suspensions, e.g. sterile injectable aqueous solutions. Rectal pharmaceutical compositions may be in the form of, for example, suppositories.

Oral pharmaceutical compositions may contain excipients such as sweetening agents, aromas, dyes, and conserving agents to provide an elegant and palatable preparation. Tablets may contain conventional pharmaceutical excipients e.g. inert diluents, e.g. calcium carbonate and lactose, dispersing agents like starch or alginic acid, binding agents such as starch, polyvinylpyrrolidone, gelatin, lubricating agents such as magnesium stearate, stearic acid and talc.

The tablets may be coated in conventional manner to delay disintegration and resorption in the gastrointestinal tract and thereby to prolong activity.

Suspensions, sirups and elixirs may contain the conv ntional excipients, e.g. suspending ag nts like methyl cellulose, tragacanth and sodium alginate, wetting agents such as lecithin,

polyoxyethylene stearate, and polyoxyethylene sorbitan monooleate and conserving agents such as ethyl parahydroxy benzoate. Capsules may contain the compound mixed for example with an solid dilu nt such as lactose, starch and a lubricating agent such as magnesium stearate.

The pharmaceutical compositions may contain up to 90% by weight of the compound as active agent.

Preferred compositions are solid dosage forms, e.g. tablets or capsules.

Representative formulations are as follows:–

Capsules

Constituent	Weight
Compound of the invention,e.g 2-ethyl-8-cyclopropylmethyl-2,8-diazaspiro(4,5)decan-1,3-dione	1 mg
Lactose	133.5 mg
Corn starch	92 mg
Silica (e.g.Aerosil 200 - Registered Trademark)	1.2 mg
Magnesium stearate	2.3 mg
	230 mg

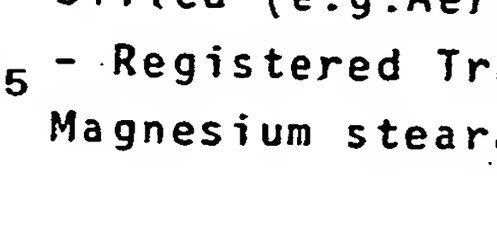
The constituents are mixed and filled into capsules.

Ampoules

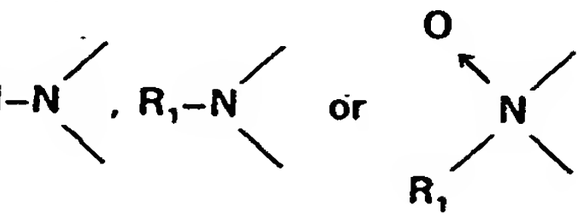
Constituent		Weight
Compound of the invention, e.g. 2,8-dimethyl-2,8-diazaspiro(4,5)decan-1,3-dione		10 mg
Sodium chloride		8 mg
Water for injectable solutions	qu.s.bis	1 ml

The ampoules were filled with 1 ml solution, closed and sterilized at 121°C for 15 minutes.

Thus in a further aspect the present invention provides a pharmaceutical composition comprising a compound of formula B



B

wherein A is 

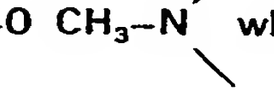
R_1 is (C_{1-6})alkyl, (C_{1-6})alkyl substituted by 1 to 6 halogens of atomic number from 9 to 35, (C_{3-6})alkenyl r-alkinyl, wherein th multiple bond is not adjacent to the nitrog n atom, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl(C_{1-2})alkyl, (C_{3-7})cycloalkyl(C_{1-2})alkyl substituted by hydroxy,

(C_{1-4})alkoxy or (C_{2-5})alkanoyl, benzyl, tetrahydrobenzocycloheptenyl or a group of formula

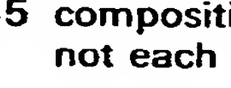
$-(CH_2)_r-X$

wherein r is 1, 2 or 3 or alternatively also O when A is R_1-N, and

X is hydroxy, mercapto, amino, (C_{1-4})alkoxy, phenoxy, benzoxy, (C_{1-4})alkylthio, phenylthio, benzylthio, (C_{1-4})alkylamino, phenylamino, benzylamino, cyano, formyl, carbamoyl, carbamoyl mono- or independently di-substituted by phenyl or (C_{1-4})alkyl,



sulfamoyl, sulfamoyl mono- or independently di-substituted by phenyl or (C_{1-4})alkyl, guanyl,



(C_{2-5})alkanoyl, (C_{2-5})alkanoyl independently substituted by 1 to 3 halogen atoms of atomic number from 9 to 35 or 2-oxo-pyrrolidinyl, benzoyl, cinnamoyl, nicotinoyl, dihydronicotinoyl, N-(C_{1-4})alkyl dihydronicotinoyl, alkoxycarbonyl with 2 to 5 carbon atoms, benzoxycarbonyl, (C_{1-4})alkoxyoxalyl, (C_{1-4})alkanoyloxy or benzoyloxy,

R_2 is hydrogen, (C_{1-6})alkyl, (C_{1-6})alkyl substituted by 1 to 6 halogen atoms of atomic number of 9 to 35, hydroxy(C_{1-4})alkyl, (C_{1-4})alkoxy(C_{1-4})alkyl, (C_{1-4})mercaptoalkyl, (C_{1-4})alkylthio(C_{1-4})alkyl, amino(C_{1-4})alkyl, mono- or independently di-(C_{1-4})alkylamino(C_{1-4})alkyl, (C_{3-6})alkenyl or alkinyl wherein the multiple bond is not adjacent to the nitrogen atom, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl(C_{1-2})alkyl, phenyl or benzyl,

R_3 is hydrogen, (C_{1-4})alkyl, benzyl or benzyl substituted by halogen of atomic number of from 9 to 35 or methoxy,

R_4 and R_5 independently are hydrogen or (C_{1-4})alkyl,

X_1 and X_2 are independently oxygen or sulphur,

m and n independently are 1, 2, 3 or 4 with the proviso that m + n is not more than 6 wherein A is other than

CH_3-N when R_2 is ethyl, R_3, R_4 and R_5 are each hydrogen, X_1 and X_2

are each hydrogen, and m and n each 2 or a pharmaceutically acceptable acid addition salt thereof in admixture with a pharmaceutical carrier or diluent, preferably a pharmaceutical composition comprising a compound of formula B as defined with the proviso that X_1 and X_2 are not each oxygen, when m and n are each 2,

A is HN or R_1-N, wherein R_1 is unsubstituted alkyl, allyl,

benzyl or benzoylalkyl, R_1 is hydrogen, unsubstituted alkyl, allyl, phenyl or benzyl or a pharmaceutically acceptable acid addition salt thereof.

In the following Examples all temperatures are uncorrected and are in degrees Centigrade.

EXAMPLE1:

2-ethyl-8-cyclopropylmethyl-2,8-diazaspiro-(4,5)decan-1,3-dione-8-oxide (process a)

A solution of 15.6 g 2-ethyl-8-cyclopropylmethyl-2,8-diazaspiro(4,5)decan-1,3-dione (produced e.g. according to Example 27) in 100 ml chloroform at 0 to 5° is treated over 30 minutes with 37.8 g m-chloroperbenzoic acid in 300 ml chloroform. The yellow solution is stirred for 20 hours at room temperature, treated with 600 ml chloroform and shaken with 200 ml 5N potassium carbonate solution. The aqueous phase is separated and extracted twice with chloroform. The combined aqueous phas s are washed with aqueous saturated sodium chloride solution, dried over sodium sulphat and concentrated to a brown oil. Chromatography on a tenfold amount of silicagel using m thylene chloride/10% methanol/1% ammonia yi lds a

yellow oil, which is converted into the crystalline hydrochloride of the title compound. Mpt. (C_2H_5OH/ether) 179–180°.

In analogous manner to example 1 the following compounds are made.

EXAMPLE 2:

2-ethyl-8-methyl-2,8-diazaspiro(4,5)decan-1,3-dione-8-oxide

Mpt. of hydrochloride: 238–239°.

EXAMPLE 3:

2-(2-methoxyethyl)-8-methyl-2,8-diazaspiro(4,5)decan-1,3-dione-8-oxide

Mpt. of hydrochloride: 204–206°.

EXAMPLE 4:

2-etyl-8-methyl-2,8-diazaspiro(4,5)decan-1,3-dithione, 2-ethyl-8-methyl-2,8-diazaspiro-(4,5)decan-1-thion-3-one and 2-ethyl-8-methyl-2,8-diazaspiro(4,5)decan-1-on-3-thione (process b)

8.7 g 2-ethyl-8-methyl-2,8-diazaspiro-(4,5)decan-1,3-dione and 12.1 g Lawesson Reagent (see above) in 100 ml toluene are boiled in 100 ml toluene for 20 hours. The solvent is then evaporated off and the residue taken up in methylene chloride. The organic phase is washed with 2N sodium carbonate solution and ice water, dried over sodium sulphate, filtered and concentrated. The yellow residue is chromatographed on a 100 fold amount of silicagel using as eluant methylene chloride containing 2% methanol and 0.2% ammonia. The title compounds are eluted in the following order in a rate of 2:1:1 and characterised as the hydrochloride salt:

2-ethyl-8-methyl-2,8-diazaspiro-(4,5)decan-1,3-dithione hydrochloride: Mpt. 257–260°.

2-ethyl-8-methyl-2,8-diazaspiro-(4,5)decan-1-thion-3-one hydrochloride: Mpt. 307–310°.

2-ethyl-8-methyl-2,8-diazaspiro-(4,5)decan-1-on-3-thione hydrochloride: Mpt. 214–215°.

EXAMPLE 5:

2-ethyl-2,7-diazaspiro(4,5)decan-1,3-dione (process c)

10 g [3-ethoxycarbonyl-3-piperidyl]-acetic acid ethyl ester and 200 ml anhydrous ethylamine, are treated at 180° for 12 hours in a steel autoclave. The excess amine is removed by a water pump vacuum at 40°C. The residue is chromatographed in a 25 fold amount of silicagel using as eluant methylene chloride containing 5% methanol/1% ammonia. The title compound is crystallised as the hydrogen maleate. Mpt. 177–180°.

The starting material is produced as follows:–

(a) *1-ethoxycarbonyl-3-piperidylidene-malonic acid diethyl ester*

100 g N-ethoxycarbonyl-piperidin-3-one and then 98.6 g malonic acid diethyl ester are added to a well stirred suspension of 3.5 litres tetrahydrofuran and 135 ml titanium tetrachloride at 0°. 185 ml pyridine are added over 30 minutes. The reaction mixture is stirred vigorously for 20 hours at room temperature.

The solvent is removed by a rotatory evaporator. The residue is treated with ice-water, dissolved in ether, and washed first with acid (2N HCl) and then sodium bicarbonate solution (10%). The ether solution is dried with sodium sulphate and treated with active charcoal. The ether is removed to give an orange brown syrup which is purified by quick chromatography through silicagel using ether as eluant. The resultant yellow oil of the heading compound is used in the next step as such.

(b) *1-ethoxycarbonyl-3-cyano-3-piperidyl-malonic acid diethyl ester*

50 g of the product obtained from step (a) is dissolved in 350 ml ethanol and treated with 9.6 g acetic acid. A solution of 15.7 g sodium cyanide in 95 ml water is added dropwise at room temperature. The mixture is stirred for 90 minutes, treated with 2N HCl solution, and concentrated on a rotary evaporator. The residue is extracted with ether. The organic phase is washed neutral and dried. The ether is removed to give a yellow oil of the heading compound which is used in the next stage as such.

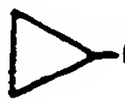
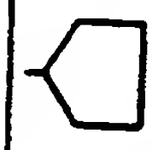
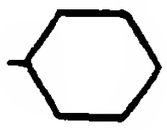
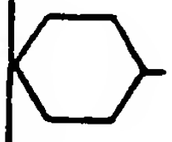
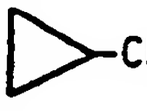
(c) *(3-ethoxycarbonyl-3-piperidyl)-acetic acid ethyl ester*

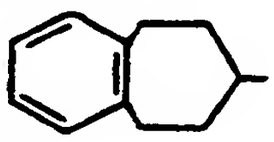
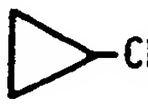
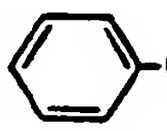
50 g of the product obtained in step (b) in 160 ml ethanol/water (1:2) at 60° are treated over 45 minutes with 230 ml concentrated hydrochloric acid. The mixture is boiled for 20 hours under reflux and then concentrated (after hydrolysis and decarboxylation) in a vacuum at 60° (bath temperature). The residue is used for the n xt stage as such or esterified with 65 ml ethanolic hydrochloric acid for 5 hours under reflux. After the reaction the solvent is removed at 60° (bath temperatur). To work up, th residue is taken up in methylene chloride that contains 5% methanol, extracted twice with 2N sodium carbonat , wash d neutral, dried over sodium sulphate, filtered and evaporated on a rotary evaporator. An orange oil of the ester heading compound is obtained.

In analogous manner to Example 5 the following compounds wherein A is

H–N (designated H h reinafter) or R_1N and X_1 and X_2

are both oxygen are obtained:–

Ex	R_1 or H	R_2	R_3	R_4	R_5	m	n	Salt form	mpt.
6		$-CH_2-CH_3$	H	H	H	2	2	hml	163-165°
7	CH_3-	$-CH_2-CH_3$	H	H	H	3	1	ch	273-276°
8	CH_3-		H	H	H	2	2	hml	171-173°
9	CH_3-		H	H	H	2	2	hml	162-163°
10	CH_3-	$-(CH_2)_3-N(CH_3)_2$	H	H	H	2	2	dch	284°
11		$-CH_2-CH_3$	H	H	H	2	2	hml	206-207°
12		$-CH_3$	H	H	H	2	2	hml	187-189°
13	$CH\equiv C-CH_2-$	$-CH_2-CH_3$	H	H	H	2	2	b	102-104°

Ex.	R_1 or H	R_2	R_3	R_4	R_5	m	n	Salt form	Mpt.
14		$-CH_2-CH_3$	H	H	H	2	2	ch	268°
15	CH_3-	$-CH_2-CH_2-OCH_3$	H	H	H	2	2	ms	201-201°
16	CH_3-	$-CH_2-CH_2-OH$	H	H	H	2	2	hb	281-282°
17		$-CH_2-CH_3$	H	H	H	2	2	ch	191-193°
18	H	$-CH_2-CF_3$	H	H	H	2	2	ch	217-220°
19	CH_3	$-CH_2-CF_3$	H	H	H	2	2	ch	269-272°
20	$-CH_2-CH_3$	$-CH_2-CF_3$	H	H	H	2	2	ch	178-181°
21		$-CH_2-CF_3$	H	H	H	2	2	ch	202-205°
22	CF_3-CH_2-	$-CH_2-CH_3$	H	H	H	2	2	ch	191-195°
23	$Cl-CH_2-CH_2-$	$-CH_2-CH_3$	H	H	H	2	2	ch	140-142°
24	CH_3-	CH_3-	H	H	H	3	2	hb	199-202°
25	H	CH_3-	H	H	H	3	2	nds	293-295°
26		$-CH_2-CF_3$	H	H	H	2	2	b	123-126°

* b = base
ch = hydrochloride
dch = dihydrochloride
hb = hydrobromide
ms = methanesulfonate
hml = hydrogen maleate
nds = naphthalene[bis][base] disulfonate[1,8]

EXAMPLE 27:

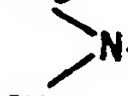
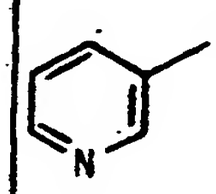
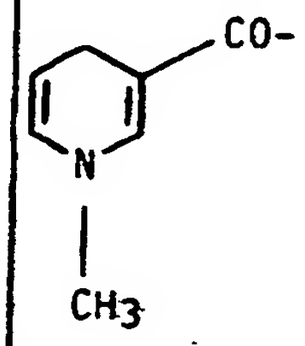
2-ethyl-8-cyclopropylmethyl-2,8-diazaspiro-(4,5)decan-1,3-dione (process d)

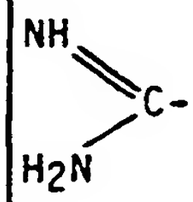
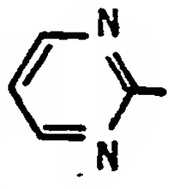
A suspension of 23.3 g 2-ethyl-2,8-diazaspiro(4,5)decan-1,3-dione, 20.6 g cyclopropylmethylbromide, 27.6 g potassium carbonate and 18.3 g potassium iodide in 500 ml dimethylformamide are stirred for 2 hours at 80°. The mixture is concentrated and the residue partitioned between water and methylene chloride. The aqueous phase is separated off and extracted twice with methylene chloride. The combined organic phases are washed with a little water, dried over sodium sulphate and concentrated to a yellow oil. Chromatography on a 20-fold amount of silicagel with methylene chloride containing 2% methanol as eluant gives the title compound as a yellow oil which is converted into the hydrogen maleate. Mpt. 163–5°.

In analogous manner to Example 27, the compounds of examples 6–17, 19–24 and 26 as well as the following compounds of formula I wherein A is

R_1-N and X_1 and X_2 are both oxygen are produced:–

Ex.	R_1	R_2	R_3	R_4	R_5	m	n	Salt form	Mpt.
28	CH_3 $N-CO-CH_2-$ CH_3	$-CH_2-CH_3$	H	H	H	2	2	hml	155-157°
29	OHC-	$-CH_2-CH_3$	H	H	H	2	2	n	142-144°
30	NC-	$-CH_2-CH_3$	H	H	H	2	2	n	125-126°

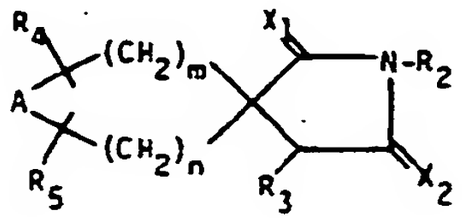
Ex.	R_1	R_2	R_3	R_4	R_5	m	n	Salt form	Mpt.
31	$NC-CH_2-$	$-CH_3$	H	H	H	2	2	ch	212-214°
32	$C_2H_5O-CO-CH_2-$	$-CH_2-CH_3$	H	H	H	2	2	b	79-80°
33		$-CH_2-CH_3$	H	H	H	2	2	n	194-196°
34	OHC-	$-CH_3$	H	H	H	2	2	n	137-138°
35		$-CH_2-CH_3$	H	H	H	2	2	n	88-92°
36	H_2N-CO-	$-CH_2-CH_3$	H	H	H	2	2	n	208-209°
37	$C_2H_5-O-CO-$	$-CH_2-CH_3$	H	H	H	2	2	n	84-85°
38		$-CH_3$	H	H	H	2	2	n	210-211°
39		$-CH_2-CH_3$	H	H	H	2	2	n	156-157°
40		$-CH_2-CH_3$	H	H	H	2	2	n	122-123°
41		$-CH_2-CH_3$	H	H	H	2	2	b	130-137°

Ex.	R_1	R_2	R_3	R_4	R_5	m	n	Salt form	Mpt.
42		$-CH_2-CH_3$	H	H	H	2	2	ch	216-217°
43	$HO-CH_2-CH_2-$	$-CH_2-CH_3$	H	H	H	2	2	ch	215-218°
44	$Cl-CH_2-CO-$	$-CH_2-CH_3$	H	H	H	2	2	n	163-166°
45	$(CH_3)_3C-O-CO-$	$-CH_2-CH_3$	H	H	H	2	2	n	101-104°
46	CH_3-CO	$-CH_2-CH_3$	H	H	H	2	2	n	154-157°
47	$(CH_3)_3C-CO-$	$-CH_2-CH_3$	H	H	H	2	2	n	109-112°
48	CH_3O-CO-	$-CH_2-CH_3$	H	H	H	2	2	n	117-120°
49	CH_3-S-CH_2-	$-CH_2-CH_3$	H	H	H	2	2	ch	168-171°
50		$-CH_2-CH_3$	H	H	H	2	2	n	210-211°

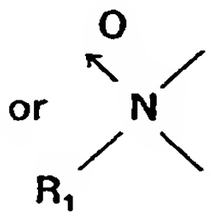
* b = base
n = neutral
ch = hydrochloride
hml = hydrogen maleate

CLAIMS

1. A process for the production of a compound of formula I



I

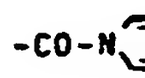
wherein A is H–N, R_1–N or 

R_1 is (C_{1-6})alkyl, (C_{1-6})alkyl substituted 1 to 6 halogens of atomic number from 9 to 35, (C_{3-6})alkenyl or-alkinyl, wherein the multiple bond is not adjacent to the nitrogen atom, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl(C_{1-2})alkyl, (C_{3-7})cycloalkyl(C_{1-2})alkyl substituted by hydroxy, (C_{1-4})alkoxy or (C_{2-5})alkanoyl, benzyl, tetrahydrobenzocycloheptenyl or a group of formula

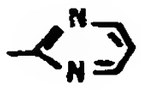
$-(CH_2)_r-X$

wherein r is 1, 2 or 3 or alternatively also O when A is R_1–N, and

X is hydroxy, mercapto, amino, (C_{1-4})alkoxy, phenoxy, benzoxy, (C_{1-4})alkylthio, phenylthio, benzylthio, (C_{1-4})alkylamino,phenylamino,benzylamino, cyano, formyl, carbamoyl, carbamoyl mono- or independently di-substituted by phenyl or (C_{1-4})alkyl,



sulfamoyl, sulfamoyl mono- or independently di-substituted by phenyl or (C_{1-4})alkyl, guanyl,



(C_{2-5})alkanoyl, (C_{2-5})alkanoyl independently substituted by 1 to 3 halogen atoms of atomic number from 9 to 35 or 2-oxo-pyrrolidinyl, benzoyl, cinnamoyl, nicotinoyl, dihydronicotinoyl, N-(C_{1-4})alkyl dihydronicotinoyl, alkoxycarbonyl with 2 to 5 carbon atoms, benzoxycarbonyl, (C_{1-4})alkoxyoxalyl, (C_{1-4})alkanoyloxy or benzoyloxy,

R_2 is hydrogen, (C_{1-6})alkyl, (C_{1-6})alkyl substituted by 1 to 6 halogen atoms of atomic number of 9 to 35, hydroxy(C_{1-4})alkyl, (C_{1-4})alkoxy(C_{1-4})alkyl, (C_{1-4})mercaptoalkyl, (C_{1-4})alkylthio(C_{1-4})alkyl, amino(C_{1-4})alkyl, mono- or independently di-(C_{1-4})alkylamino(C_{1-4})alkyl, (C_{3-6})alkenyl or alkinyl wherein the multiple bond is not adjacent to the nitrogen atom, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl(C_{1-2})alkyl, phenyl or benzyl,

R_3 is hydrogen, (C_{1-4})alkyl, benzyl or benzyl substituted by halogen of atomic number of from 9 to 35 or methoxy,

R_4 and R_5 independently are hydrogen or (C_{1-4})alkyl,

X_1 and X_2 are independently oxygen or sulphur,

m and n independently are 1,2, 3 or 4 with the proviso that m + n is not more than 6 with the proviso that X_1 and X_2 are not both oxygen when m and n are each 2,

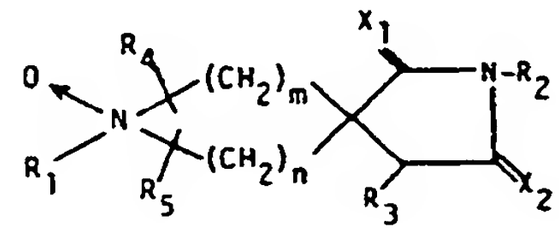
A is N–N or R_1–N wherein R_1 is unsubstituted (C_{1-6})alkyl,

chloropropyl, hydroxypropyl, allyl, b nzyl, ethoxycarbonyl, b nzoylalkyl and R_2 is hydrog n, unsubstituted (C_{1-6})alkyl, allyl, phenyl, or benzyl,

or an acid addition salt thereof,

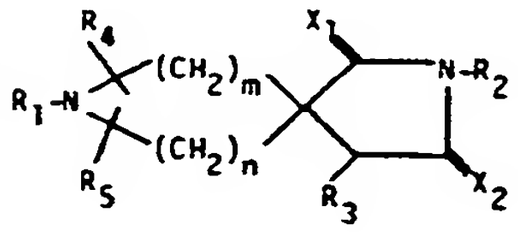
which comprises

(a) for the production of a compound of formula Ia



Ia

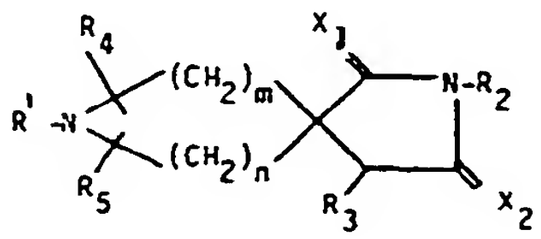
wherein R_{1-5}, X_1, X_2, m and n are as defined above, or an acid addition salt thereof, oxidizing an appropriate compound of formula II



II

wherein R_{1-5}, X_1, X_2, m and n are as defined above, or an acid addition salt thereof,

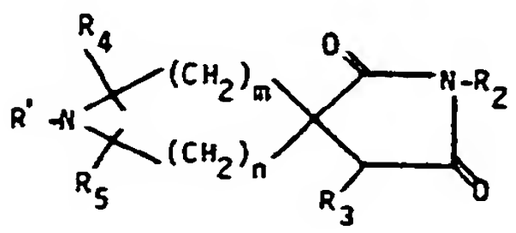
(b) for the production of a compound of formula Ib



Ib

wherein R′ is hydrogen or R_1 as defined above, and R_{2-5}, X_1, X_2, m and n are as defined above with the provisos thereto and the further proviso that both X_1 and X_2 are not oxygen, or an acid addition salt thereof,

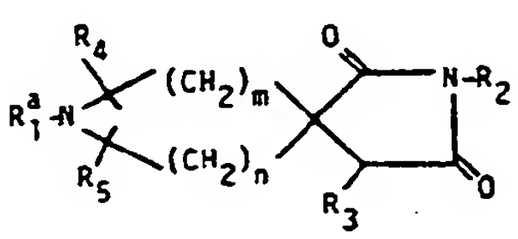
replacing at least one oxo group by a thio group in an appropriate compound of formula III



III

wherein R′, R_5, m and n are as defined above or an acid addition salt thereof,

(c) for the production of a compound of formula Ic



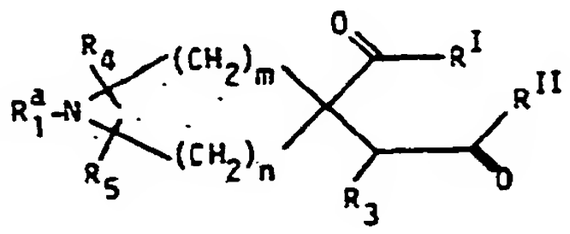
Ic

wherein R_{2-5}, m and n are as defined above, and R_1^a is hydrogen, (C_{1-6})alkyl,(C_{1-6})alkyl substituted by 1 to 6 halogens of atomic number of from 9 to 35, (C_{3-6})alkenyl or-alkinyl, wherein the multiple bond is not adjacent to the nitrogen atom, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl (C_{1-2})alkyl, (C_{3-7})cycloalkyl(C_{1-2})alkyl substituted by hydroxy, (C_{1-4})alkoxy or (C_{2-5})alkanoyl, benzyl, or tetrahydrobenzocycloheptenyl,

with the proviso that m and n are not both 2 when R_1^a is hydrogen, unsubstituted (C_{1-6})alkyl,hydroxypropyl,chloropropyl, allyl or benzyl and R_2 is hydrogen, (C_{1-6})alkyl, allyl, phenyl or benzyl,

or an acid addition salt thereof,

cyclising the product obtainable by condensing a compound of formula IV

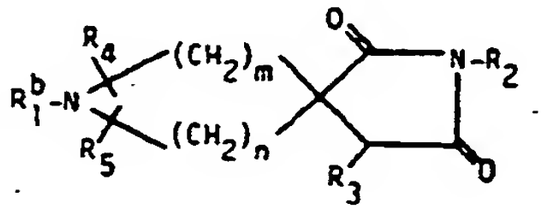


wherein R_1^a, R_{3-5}, m and n are as defined above with respect to formula Ic, and R^I and R^{II} are independently leaving groups, with an appropriate compound of formula V

R_2-NH_2 V

wherein R_2 is as defined above with respect to formula Ic,

(d) for the production of a compound of formula Id



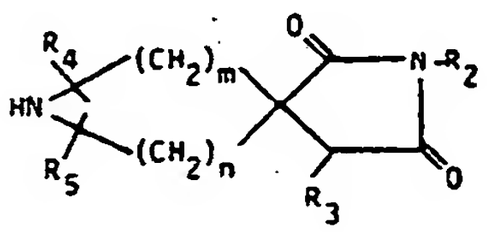
Id

wherein R_{2-5}, m and n are as defined above and

R_1^b is as defined above for R_1 with the proviso that m and n are not both 2 when R_1^b is unsubstituted (C_{1-6})alkyl, hydroxypropyl, chloropropyl, allyl, benzyl, ethoxycarbonyl or benzoylalkyl and R_2 is hydrogen, unsubstituted (C_{1-6})alkyl, allyl, phenyl or benzyl,

or an acid addition salt thereof,

introducing a group of formula R_1^b into a compound of formula VI



VI

wherein R_{2-5}, m and n are as defined above with respect to formula Id, and recovering the compound of formula I or an acid addition salt thereof.

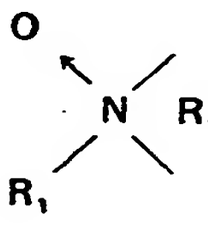
2. A process for the production of a compound of formula I or an acid addition salt thereof substantially as hereinbefore described.

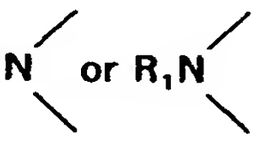
3. A compound of formula I or an acid addition salt thereof whenever produced by the process of claim 1 or 2.

4. A compound of formula I or an acid addition salt thereof as defined in claim 1.

5. A compound of claim 4 wherein A is as defined in claim 1, R_1 is (C_{1-4})alkyl, (C_{1-4})alkyl substituted by 1 to 6 halogen atoms of atomic number from 9 to 35, cyclopropylmethyl, (C_{3-7})cycloalkyl, cyano, cyanomethyl or formyl, R_2 is hydrogen, (C_{1-4})alkyl, (C_{1-4})alkyl substituted by 1 to 6 halogen atoms of atomic number from 9 to 35, or (C_{3-7})cycloalkyl, R_3, R_4 and R_5 are each hydrogen, X_1 and X_2 are independently oxygen or sulphur, m and n are each 2,

with the provisos that

(i) when A is  R_1 is other than cyano or formyl, and

(ii) X_1 and X_2 are not both oxygen when A is  or R_1N

wherein R_1 is unsubstitut d alkyl or chloropropyl and R_2 is hydrog n or unsubstituted alkyl, or an acid addition salt thereof.

6. A compound of claim 4 which is 2-ethyl-8-cyclopropylmethyl-2,8-diazaspiro(4,5)-decan-1,3-dione-8-oxide or an acid additi n salt thereof.

7. A compound of claim 4 which is 2-ethyl-8-methyl-2,8-diazaspiro(4,5)decan-1,3-dione-8-oxide or an acid addition salt thereof.

8. A compound of claim 4 which is 2-(2-methoxyethyl)-8-methyl-2,8-diazaspiro(4,5)decan-1,3-dione-8-oxide or an acid addition salt ther of.

9. A compound of claim 4 which is 2-ethyl-8-methyl-2,8-diazaspiro-(4,5)decan-1,3-dithione or an acid addition salt thereof.

10. A compound of claim 4 which is 2-ethyl-8-methyl-2,8-diazaspiro-(4,5)decan-1-thion-3-one or an acid addition salt thereof.

11. A compound of claim 4 which is 2-ethyl-8-methyl-2,8-diazaspiro-(4,5)decan-1-one-3-thione or an acid addition salt thereof.

12. A compound of claim 4 which is 2-ethyl-2,7-diazaspiro-(4,5)decan-1,3-dione or an acid addition salt thereof.

13. A compound of claim 4 which is 2-ethyl-8-cyclopropylmethyl-2,8-diazaspiro-(4,5)decan-1,3-dione or an acid addition salt thereof.

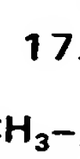
14. A compound of formula I wherein A is R_1N, X_1 and X_2 are both oxygen, R_1 is

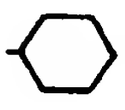
R_2 is $-CH_2-CH_3$, R_3, R_4 and R_5 each are hydrogen, m and n each two or an acid addition salt thereof.

15. A compound of formula I wherein A is R_1N  , X_1 and X_2 are both oxygen, R_1 is CH_3-, R_2 is $-CH_2-CH_3$, R_3, R_4 and R_5 are each hydrogen, m is 3, n is 1 or an acid addition salt thereof.

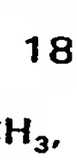
16. A compound of formula I wherein A is R_1N  , X_1 and X_2 are both oxygen, R_1 is CH_3, R_2 is

R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

17. A compound of formula I wherein A is R_1N  , X_1 and X_2 are both oxygen, R_1 is CH_3-, R_2 is



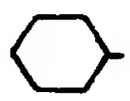
R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

18. A compound of formula I wherein A is R_1N  , X_1 and X_2 are both oxygen, R_1 is CH_3,

R_2 is $-(CH_2)_3-N(CH_3)_2$,

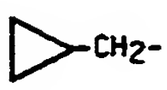
R_3, R_4 and R_5 are each hydrogen, m and n two or an acid addition salt thereof.

19. A compound of formula I wher in A is R_1N  , X_1 and X_2 are both oxygen, R_1 is



R_2 is $-CH_2-CH_3$, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

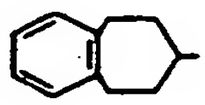
20. A compound of formula I wherein A is R_1N  , X_1 and X_2 are both oxygen, R_1 is



R_2 is $-CH_3$, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

21. A compound of formula I wherein A is R_1N  , X_1 and X_2 are both oxygen, R_1 is $CH{\equiv}C-CH_2-$, R_2 is $-CH_2-CH_3$, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

22. A compound of formula I wherein A is R_1N , X_1 and X_2 are both oxygen, R_1 is

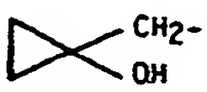


R_2 is $-CH_2-CH_3$, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

23. A compound of formula I wherein A is R_1N  , X_1 and X_2 are both oxygen, R_1 is CH_3-, R_2 is $-CH_2-CH_2-OCH_3$, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

24. A compound of formula I wherein A is R_1N  , X_1 and X_2 are both oxygen, R_1 is CH_3-, R_2 is $-CH_2-CH_2-OH$, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

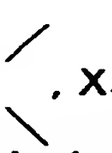
25. A compound of formula I wherein A is R_1N  , X_1 and X_2 are both oxygen, R_1 is



R_2 is $-CH_2-CH_3$, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

26. A compound of formula I wherein A is HN  , X_1 and X_2 are both oxygen, ——R_2 is $-CH_2-CF_3$, r_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

27. A compound of formula I wherein A is R_1N  , X_1 and X_2 are both oxygen, R_1 is CH_3, R_2 is $-CH_2-CF_3$, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

28. A compound of formula I wherein A is R_1N  , X_1 and X_2 are both oxygen, R_1 is $-CH_2-CH_3$, R_2 is $-CH_2-CF_3$, R_3, R_4 and R_5 are ach hydrogen, m and n each two or an acid addition salt thereof.

29. A compound of formula I wherein A is R_1N , X_1 and X_2 are both oxygen, R_1 is

R_2 is $-CH_2-CF_3$, R_3, R_4 and R_5 are each hydrogen, m an n each two or an acid addition salt thereof.

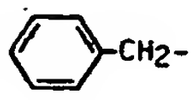
30. A compound of formula I wherein A is R_1N , X_1 and X_2 are both oxygen, R_1 is CF_3-CH_2-, R_2 is $-CH_2-CH_3$, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

31. A compound of formula I wherein A is R_1N , X_1 and X_2 are both oxygen, R_1 is $Cl-CH_2-CH_2-$, R_2 is $-CH_2-CH_3$, R_3, R_4 and R_5 are each hydrogen, n and n each two or an acid addition salt thereof.

32. A compound of formula I wherein A is R_1N , X_1 and X_2 are both oxygen, R_1 is CH_3-, R_2 is CH_3-, R_3, R_4 and R_5 are each hydrogen, m is 3, n is 2 or an acid addition salt thereof.

33. A compound of formula I wherein A is HN , X_1 and X_2 are both oxygen, R_2 is CH_3, R_3, R_4 and R_5 are each hydrogen, m is 3, n is 2 or an acid addition salt thereof.

34. A compound of formula I wherein A is R_1N , X_1 and X_2 are both oxygen, R_1 is



R_2 is $-CH_2-CF_3$, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

35. A compound of formula I wherein A is R_1N , X_1 and X_2 are both oxygen,

are both oxygen, R_1 is $N-CO-CH_2-$, R_2 is $-CH_2-CH_3$, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

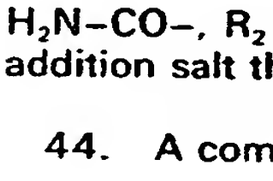
36. A compound of formula I wherein A is R_1N , X_1 and X_2 are both oxygen, R_1 is OHC–, R_2 is $-CH_2-CH_3$, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

37. A compound of formula I wherein A is R_1N , X_1 and X_2 are both oxygen, R_1 is NC–, R_2 is $-CH_2-CH_3$, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

38. A compound of formula I wher in A is R_1N , X_1 and X_2 are both oxygen, R_1 is $NC-CH_2-$, R_2 is $-CH_3$, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

39. A compound of formula I wherein A is R_1N , X_1 and X_2 are both oxygen, R_1 is $C_2H_5O-CO-CH_2-$, R_2 is $-CH_2-CH_3$, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

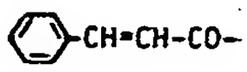
40. A compound of formula I wherein A is R_1N , X_1 and X_2 are both oxygen, R_1 is



R_2 is $-CH_2-CH_3$, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

41. A compound of formula I wherein A is R_1N , X_1 and X_2 are both oxygen, R_1 is OCH–, R_2 is $-CH_3$, R_3, R_4 and R_5 are each hydrogen, m an n each two or an acid addition salt thereof.

42. A compound of formula I wherein A is R_1N , X_1 and X_2 are both oxygen, R_1 is

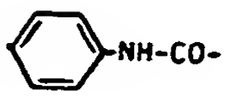


R_2 is $-CH_2-CH_3$, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

43. A compound of formula I wherein A is R_1N , X_1 and X_2 are both oxygen, R_1 is H_2N-CO-, R_2 is $-CH_2-CH_3$, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

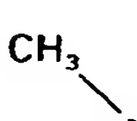
44. A compound of formula I wherein A is R_1N , X_1 and X_2 are both oxygen, R_1 is $C_2H_5-O-CO-$, R_2 is $-CH_2-CH_3$, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

45. A compound of formula I wherein A is R_1N , X_1 and X_2 are both oxygen, R_1 is



R_2 is CH_3, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

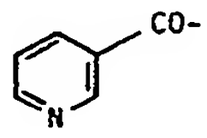
46. A compound of formula I wherein A is R_1N , X_1 and X_2 are both oxygen, R_1 is



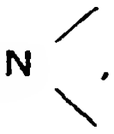
$N-SO_2$, R_2 is $-CH_2-CH_3$, R_3, R_4 and R_5 are each hydrogen,

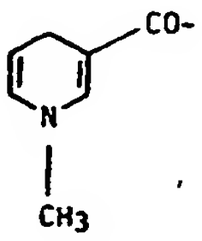
m and n each two or an acid addition salt thereof.

47. A compound of formula I wherein A is R_1N , X_1 and X_2 are both oxygen, R_1 is



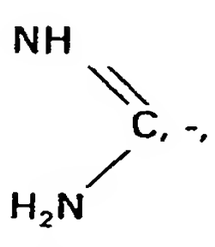
R_2 is $-CH_2-CH_3$, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

48. A compound of formula I wherein A is R_1N  , X_1 and X_2 are both oxygen, R_1 is

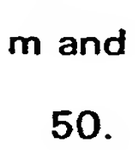


R_2 is $-CH_2-CH_3$, R_3, R_4 R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

49. A compound of formula I wherein A is R_1N  , X_1 and X_2 are both oxygen, R_1 is



, R_2 is $-CH_2-CH_3$, R_3, R_4 and R_5 are each hydrogen,

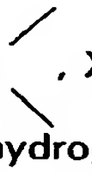


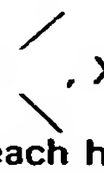
m and n each two or an acid addition salt thereof.

50. A compound of formula I wherein A is R_1N  , X_1 and X_2 are both oxygen, R_1 is $OH-CH_2-CH_2$, R_2 is $-CH_2-CH_3$, R_3, R_4 and R_5 are both oxygen, m and n each two or an acid addition salt thereof.

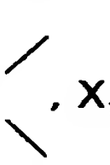
51. A compound of formula I wherein A is R_1N  , X_1 and X_2 are both oxygen, R_1 is $Cl-CH_2-CO-$, R_2 is $-CH_2-CH_3$, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

52. A compound of formula I wherein A is R_1N  , X_1 and X_2 are both oxygen, R_1 is $(CH_3)_3C-O-CO-$, R_2 is $-CH_2-CH_3$, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

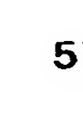
53. A compound of formula I wherein A is R_1N  , X_1 and X_2 are both oxygen, R_1 is CH_3-CO, R_2 is $-CH_2-CH_3$, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

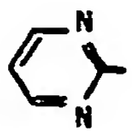
54. A compound of formula I wherein A is R_1N  , X_1 and X_2 are both oxygen, R_1 is $(CH_3)_3C-CO-$, R_2 is $-CH_2-CH_3$, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

55. A compound of formula I wherein A is R_1N  , X_1 and X_2 are both oxygen, R_1 is CH_3O-CO, R_2 is $-CH_2-CH_3$, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

56. A compound of formula I wherein A is R_1N  , X_1 and X_2 ar both oxygen, R_1 is

CH_3–S–CH_2–, R_2 –CH_2–CH_3, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

57. A compound of formula I wherein A is R_1N  , X_1 and X_2 are both oxygen, R_f is



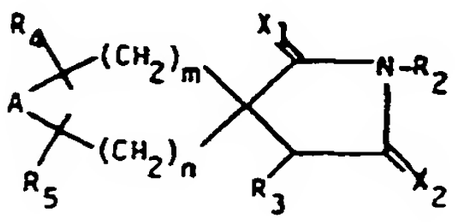
R_2 is –CH_2–CH_3, R_3, R_4 and R_5 are each hydrogen, m and n each two or an acid addition salt thereof.

58. A compound of any one of claims 3 to 57 or a pharmaceutically acceptable acid addition salt thereof for use as a pharmaceutical.

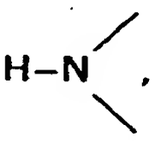
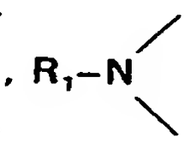
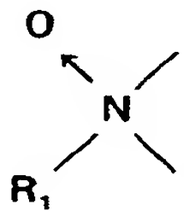
59. A compound of any one of claims 3 to 57 or a pharmaceutically acceptable acid addition salt thereof for use in the treatment of senile dementia, Alzheimer's disease, Huntington's chorea, tardive diskinesia or hyperkinesia, or mania.

60. A pharmaceutical composition comprising a compound of any one of claims 3 to 57 or a pharmaceutically acceptable acid addition salt thereof in association with a pharmaceutical carrier or diluent.

61. A pharmaceutical composition comprising a compound of formula B

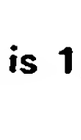


B

wherein A is  , R_1–N  or 

R_1 is (C_{1-6})alkyl, (C_{1-6})alkyl substituted by 1 to 6 halogens of atomic number from 9 to 35, (C_{3-6})alkenyl or alkinyl, wherein the multiple bond is not adjacent to the nitrogen atom, (C_{3-7})cycoalkyl, (C_{3-7})cycloalkyl(C_{1-2})alkyl, (C_{3-7})cycloalkyl(C_{1-2})alkyl substituted by hydroxy, (C_{1-4})alkoxy or (C_{2-5})alkanoyl, benzyl, tetrahydrobenzocloheptenyl or a group of formula

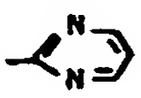
–(CH_2)$_r$–X

wherein r is 1, 2 or 3 or alternatively also O when A is R_1–N  , and

X is hydroxy, mercapto, amino, (C_{1-4})alkoxy, phenoxy, benzoxy, (C_{1-4})alkylthio, phenylthio, benzylthio, (C_{1-4})alkylamino-phenylamino,benzylamino, cyano, formyl, carbamoyl, carbamoyl mono- or independently di-substituted by phenyl or (C_{1-4})alkyl,

-CO-N  ,

sulfamoyl, sulfamoyl mono- or independently di-substituted by phenyl or (C_{1-4})alkyl, guanyl,



(C_{2-5})alkan yl, (C_{2-5})alkanoyl independently substituted by 1 to 3 halogen atoms of atomic number from 9 to 35 or 2-oxo-pyrrolidinyl, benzoyl, cinnamoyl, nicotinoyl, dihydronicotinoyl, N-(C_{1-4})alkyl dihydronicotinoyl, alkoxycarbonyl with 2 to 5 carbon atoms, benzoxycarbonyl,

(C_{1-4})alkoxyoxalyl, (C_{1-4})alkanoyloxy or benzoyloxy,

R_2 is hydrogen, (C_{1-6})alkyl, (C_{1-6})alkyl substituted by 1 to 6 halogen atoms of atomic number of 9 to 35, hydroxy(C_{1-4})alkyl, (C_{1-4})alkoxy(C_{1-4})alkyl, (C_{1-4})mercaptoalkyl, (C_{1-4})alkylthio(C_{1-4})alkyl, amino(C_{1-4})alkyl, mono- or independently di-(C_{1-4})alkylamino(C_{1-4})alkyl, (C_{3-6})alkenyl or alkinyl wherein the multiple bond is not adjac nt to the nitrogen atom, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl(C_{1-2})alkyl, phenyl or benzyl,

R_3 is hydrogen, (C_{1-4})alkyl, benzyl or benzyl substituted by halogen of atomic numb r of from 9 to 35 or methoxy,

R_4 and R_5 independently are hydrogen or (C_{1-4})alkyl,

X_1 and X_2 are independently oxygen or sulphur,

m and n independently are 1,2, 3 or 4 with the proviso that m + n is not more than 6

wherein A is other than $CH_3-N<$ when R_2 is ethyl, R_3, R_4 and R_5 are each hydrogen,

X_1 and X_2 are each oxygen, and m and n each 2 or a pharmaceutically acceptable acid addition salt thereof in admixture with a pharmaceutical carrier or diluent.

62. A pharmaceutical composition comprising a compound of formula B as defined in claim 56 with the proviso that X_1 and X_2 are not each oxygen, m and n are each 2,

A is $HN<$ or $R_1-N<$, wherein R_1 is unsubstituted (C_{1-6})alkyl,

hydroxypropyl,chloropropyl,allyl, allyl,phenyl or benzyl or a pharmaceutically acceptable acid addition salt thereof.

63. A pharmaceutical composition according to claim 59 wherein the compound is a compound of formula B wherein A, R_1, R_2, R_3, R_4, R_5, X_1, X_2, m and n are defined as in claim 61 with the proviso that X_1 and X_2 are not each oxygen, when m and n are each two,

A is $HN<$ or $R_1-N<$ wherein R_1 is unsubstituted alkyl, allyl, benzyl or benzoylallyl,

and R_2 is hydrogen, unsubstituted alkyl, allyl, phenyl or benzyl or a pharmaceutically acceptable acid addition salt thereof.

64. A pharmaceutical composition according to claim 59 wherein the compound is a compound of formula B wherein R_1 is hydroxypropyl, chloropropyl or ethoxy-carbonyl.

65. A compound of formula B as defined in claim 61, 62, 63 or 64 for use in the treatment of senile demantia, Alzheimer's disease, Huntington's chorea, tardive diskinesia or hyperkinesia, or mania.

66. A compound of formula IV as defined in claim 1 or a compound obtainable by reacting a compound of formula IV as defined in claim 1 and a compound of formula V as defined in claim 1.

67. Compounds of formula III as defined in claim 1 or an acid addition salt thereof.

68. Compounds of formula Ib as defined in claim 1 or an acid addition salt thereof.

69. Compounds of formula IA wherein R_1 is as defined in claim 1 and when it contains the group X_1 this is hydroxy, alkoxy, phenoxy, formyl, optionally substituted alkanoyl, benzoyl, cinnamoyl, alkoxycarbonyl, benzoxycarbonyl, alkanoyloxy or benzoyloxy as defined in claim 1, and R_2 is hydrogen, alkyl optionally substituted by halogen, alkoxyalkyl, hydroxyalkyl,alkenyl or alkinyl,cycloalkyl,cycloalkylalkyl,phenyl or benzyl as defined in claim 1,or an acid addition salt thereof.

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